Please amend the application as follows:

In the Specification

Please replace the paragraph at page 9, lines 16 through 17, with the following paragraph:

B1

- - - Figures 6A and 6B are tables listing the 27 genes activated by MYC and the 9 genes repressed by MYC. Relative activation and repression levels are shown. - - -

Please replace the paragraph at page 13, lines 3 through 12, with the following paragraph:

B2

- - - Using oligonucleotide microarrays to monitor the effects of induced MYC expression, 27 target genes were found that are activated by MYC and 9 target genes were found that are repressed by MYC (see Figures 6A and 6B). Based on changes in expression in the presence of cycloheximide, it was determined that most MYC target genes (18/27 of activated targets and 8/9 for repressed targets) are "direct targets," used herein to refer to target genes that are directly regulated by MYC and not by an intermediate transcription factor. This finding, coupled with the observation that none of the putative MYC target genes identified are transcription factors, argues against the idea that MYC's role is to activate a transcriptional cascade. Thus, the genes regulated by MYC are likely to be effector genes whose activities lead directly to specific cellular function. - - -

Please replace the paragraph at page 14, line 20 through page 15, line 7 with the following paragraph:

B3

- - - A major effect of MYC on both *Drosophila* and mammalian cells is to increase the accumulation of cell size (Johnston, L. *et al.*, 1999. *Cell.* 98:779-790; Iritani, B. and Eisenman, R., 1999. *Proc. Natl. Acad. Sci. USA.* 96:13180-13185). Data described herein provide support for the view that MYC directly influences cell size through protein synthesis. Earlier work had indicated that the rate-limiting translational initiation factor, EIF4E, is induced by MYC (Rosenwald, I. *et al.*, 1993. *Proc. Natl. Acad. Sci. USA.* 90:6175-6178). Work described herein

indicates that MYC induces EIF5A, a translation initiation factor also thought to be involved in nucleocytoplasmic transport (Rosorius, O. *et al.*, 1999. *J. Cell Sci.* 112:2369-2380; Elfgang, C. *et al.*, 1999. *Proc. Natl. Acad. Sci. USA.* 96:6229-6234). Interestingly, MYC leads to increased levels of the previously identified target ornithine decarboxylase (Bello-Fernandez, C. *et al.*, 1993. *Proc. Natl. Acad. Sci. USA.* 90:7804-7808; Wagner, A. *et al.*, 1993. *Cell Growth Diff.* 4:879-883; Figures 6A and 6B), which regulates a hypusine modification of EIF5A that is critical for its function (Park, M. *et al.*, 1998. *J. Biol. Chem.* 273:1677-1683). Other cell-size associated genes identified as MYC targets herein include several genes involved in nucleolar rRNA processing such as the structural proteins fibrillarin and nucleolin, the ribosomal protein RPS11, and EIF4γ. - - -

Please replace the paragraph at page 18, line 15 through page 19, line 4 with the following paragraph:

- - - A complete protocol for converting RNA into "target" suitable for hybridization to microarrays is available at the world wide web site genome.wi.mit.edu/MPR. Briefly, polyA mRNA was selected with oligo-dT beads from total RNA extracted with Trizol reagent (Life Technologies, Gaithersburg, MD), and used to create cDNA with a T7-polyT primer and the reverse transcriptase Superscript II (Gibco-BRL, Gaithersburg, MD). Approximately 1 microgram of cDNA was subjected to *in vitro* transcription in the presence of biotinylated UTP and CTP. Target for hybridization was prepared by combining 40 micrograms of fragmented transcripts with sonicated herring sperm DNA (0.1 mg/mL) and 5 nM control oligonucleotide in a buffer containing 1.0 M NaCl, 10 mM Tris-HCl (pH 7.6) and 0.005% Triton X-100. Target was hybridized for 16 hours at 40°C to a set of four oligonucleotide arrays (HUM6000-1, HUM6000-2, HUM6000-3, HUM6000-4; Affymetrix, Santa Clara, CA) containing probes for 6416 human genes (5223 known human genes and 1193 unnamed ESTs). Arrays were washed at 50°C with 6X SSPET (0.9 M NaCl, 60 mM NaH_2O_4, 6 mM EDTA, .005% Triton X-100, pH 7.6), then at 40°C with 0.5X SSPET. Arrays were then stained with streptavidin-phycoerythrein. Fluorescence intensities were captured with a laser confocal scanner (Affymetrix, Santa Clara, CA) and the Genechip software (Affymetrix, Santa Clara, CA). - - -

Please replace the paragraph at page 21, lines 11 through 18, with the following paragraph:

B5

- - - Figures 6Aand 6B summarize the 27 genes that were up-regulated and 9 genes that were down-regulated in all three MYC induction experiments. This is a significantly greater number of genes than would be expected to be induced based exclusively on fluctuations due biological or technical variability. Several other previously reported MYC targets showed some evidence of regulation but did not meet our strict criterion of 2-fold induction in all three experiments. The complete data set for all of the experiments reported herein is available at the world wide web site genome.wi.mit.edu/MPR, the teachings of which are incorporated herein by reference. - - -

Please replace the paragraph at page 21, lines 19 through 23, with the following paragraph:

B6

- - - Significantly, only two of the genes identified in Figures 6A and 6B as putative MYC target genes have been previously reported as downstream MYC targets [ODC (Bello-Fernandez, C. *et al.*, 1993. *Proc. Natl. Acad. Sci. USA.* 90:7804-7808; Wagner, A. *et al.*, 1993. *Cell Growth Diff.* 4:879-883) and nucleolin (Greasley, P. *et al.*, 1999. *Nucl. Acids Res.* 28:446-453)]. - - -

Please replace the paragraph at page 21, line 26 through page 22, line 6 with the following paragraph:

B7

- - - To discriminate between direct and indirect MYC targets, MYC-ER was activated in the presence of cycloheximide (Galaktionov, K. *et al.*, 1996. *Nature.* 382:511-517; Grandori, C. *et al.*, 1996. *EMBO J.* 15:4344-4357). By inhibiting protein synthesis, cycloheximide eliminated the possibility that MYC-induced proteins would subsequently modulate a secondary set of genes. Of the 27 genes consistently induced by MYC-ER, 18 genes (68%) were also up-regulated in the presence of cycloheximide, while almost all of the repressed genes (8/9) were

B7 also down-regulated under these conditions (Figures 6A and 6B). These results suggest that most of the targets identified are likely to be direct targets of MYC. - - -

Please replace the paragraph at page 22, lines 9 through 23, with the following paragraph:

- - - To verify induction by an independent method, six induced target genes were chosen from the set of putative MYC target genes identified in Figures 6A and 6B for Northern blot analysis. In all cases, the Northern blots confirmed the microarray results indicating up-regulation by MYC-ER. For four genes, the same RNA as was used for the microarray measurements was examined for two separate inductions, and for two genes RNA was investigated from an independent MYC-ER induction. As shown in Figures 3A-3C, FKBP52, FABP5, PPIF, EIF5A and cyclin D2 follow a similar pattern of expression to that of the known target gene ODC. The ratio of transcript levels in MYC-ER expressing fibroblasts with and without stimulation determined by Northern blot correlated well with the estimates based on the microarrays: 2.3 (Northern, exp. 1)/2.3 (microarray, exp. 1) and 2.2 (Northern, exp. 2)/2.1 (microarray exp. 2) for FKBP52; 1.8/2.0 and 1.4/2.1 for PPIF; 4.1/3.6 for FABP5; 1.8/2.3-3.0 for EIF5A and 3.5/2.2-5.7 for cyclin D2 (Figures 3A and B). Thus, the Northern blot data demonstrate an increase in expression in the same range as expected from the microarray results for all of the genes tested. - - -

B8

Please replace the paragraph at page 23, lines 6 through 19, with the following paragraph:

- - - In order to determine whether the putative targets identified in the microarray assays are influenced by changes in MYC levels under physiologically relevant conditions, it was assessed whether these targets are also affected during the shut-off of endogenous MYC which accompanies hematopoietic differentiation (Henriksson, M. and Luscher, B., 1996. *Adv. Cancer Res.* 68:109-182 1996). In Figures 6A and 6B, ratios of gene expression in differentiated and undifferentiated HL60 cells are given for each of the genes identified as a candidate MYC target in the MYC-ER experiments. Seventeen of the 27 genes consistently induced in the MYC-ER experiments showed a greater than 2-fold decline in expression as HL-60 cells differentiated,

B9